REMARKS

Status

Claims 66-68 and 73-89 are present in the application, with Claims 66-68 and 73-75 under active consideration. Claims 1-65, 69-72, and 76-80 are canceled. Claims 81-89 have been added by this Amendment. Upon entry of the claim amendments above, Claims 66, 81 and 85 are independent. Support for new Claims 81-89 is found in the specification at page 26, lines 24-25; page 62, lines 6-10; page 65, lines 1-30 and throughout the specification. The other amendments are editorial in nature or to more particularly define the invention.

Accordingly, this Amendment incorporates no new matter.

Telephone Interview

Applicant's gratefully acknowledge the Examiner's kind consideration during the Telephone Interview on May 26, 2004.

Claim Rejections under 35 U.S.C. § 102

Claims 66-68 and 73-74 are rejected under 35 U.S.C. § 102(e) as purportedly anticipated by Ishizaka et al., U.S. Patent No. 5,786,168. Applicants respectfully traverse.

Applicants respectfully point out that the claims are directed to a diagnostic method for determining the amount of macrophage migration inhibitory factor (MIF) protein in a sample, comprising: (a) obtaining a sample; and (b) determining the amount of MIF protein in the sample using an immunoassay with an anti-MIF antibody, wherein the immunoassay is selected from the group consisting of ELISA, immunoprecipitation, immunohistocytochemistry, and Western analysis, and wherein said MIF protein is the human MIF protein having a molecular weight of approximately 12.5 kDa and having MIF biological activity, and wherein the anti-MIF antibody binds to the MIF protein.

The Ishizaka et al. patent fails to disclose the invention, either expressly or inherently. Ishizaka et al. is directed to Glycosylation Inhibitory Factor (GIF) and its involvement in physiology and pathology. GIF is not Macrophage Migration Inhibitory Factor (MIF). As Ishizaka et al. states at column 2, lines 60-64, GIF is uniquely identified by its biological properties and it undergoes at least one post-translational modification in phosphorylation that is not associated with MIF when it states: "A unique property of GIF is its biochemical activity. This lymphokine binds to monoclonal antibodies against lipomodulin (a phospholipase inhibitory protein) and appears to be a phosphorylated derivative of a phospholipase inhibitory protein (Uede, et al., J. Immunol, 130: 878, 1983)." Also, GIF does not exhibit MIF biological properties as Ishizaka et al. points out at column 46: "The results indicated that rhGIF was different from MIF in biological activity." Ishizaka et al. is acknowledging in the document itself the structural and functional distinctions between GIF and MIF.

The Office Action does not establish that any element in the claim is disclosed in Ishizaka et al. In addition, the claim involves other elements than simply an antibody that binds MIF. For instance, the reference does not disclose MIF as a diagnostic target. "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). "The identical invention must be shown in as complete detail as is contained in the ... claim." *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989).

Furthermore, *assuming arguendo*, that the disclosure of merely an antibody that fell within the scope of the claim were sufficient to anticipate the claim, the Office Action is not sufficient in that there is no adequate basis to assert that an antibody that binds to GIF as in Ishizaka et al. will necessarily bind to MIF. Despite assertions in the Office Action to the

contrary, the fact that two different proteins (MIF and GIF) may share a similar sequence does not mean that an antibody to one protein will necessarily bind to the other protein. An antibody does not necessarily bind to a sequence as coded by DNA, but instead binds to the final form of the biologically active protein.

Furthermore, the sequence SEQ ID NO:38 is a "deduced" sequence taken from the DNA code for GIF. SEQ ID NO:38 does not represent the biologically active protein structure for GIF as the sequence coded by the DNA (i.e., the primary protein structure) can undergo numerous further changes (e.g. such as to the secondary, tertiary and quaternary protein structures and other modifications) that will affect the protein folding and conformation, the protein chemical structure, and the protein glycosylation patterns; all of which can affect the biological activity of the final protein molecule.

It is common knowledge that antibodies bind to proteins based not only on the primary protein structure (i.e., the linear sequence), but also based on the combination of primary, secondary, tertiary, and perhaps also, the quaternary protein structure that all contribute to the three-dimensional folding of the target protein. Just because the deduced sequence of GIF and the deduced sequence of MIF are the same does not necessarily imply that an antibody to biologically active GIF will also bind to biologically active MIF. GIF clearly has other structural distinctions without parallel in MIF such as cysteinylation, phosphorylation and complexation which ultimately affect both structure and function. Hence, one cannot reliably account for how these changes will impact the final three-dimensional structure of the GIF protein.

There are still more reasons to doubt that an antibody that binds a GIF will also bind MIF. Ishizaka et al. notes that there is more than one form of GIF, at column 2, line 67 et seq.

> "Subsequent experiments on ovalbumin (OVA)-specific suppressor T-cell hybridomas indicated that stimulation of the hybridoma cells with antigen (OVA)-

pulsed syngeneic macrophages resulted in the formation of GIF that has affinity for OVA (antigen-binding GIF). However, the same hybridomas constitutively secreted GIF having no affinity for OVA (nonspecific GIF). Studies on the relationship between nonspecific GIF and OVA-binding GIF indicated that the antigen-binding GIF is composed of an antigen-binding polypeptide chain and a nonspecific GIF."

Ishizaka et al. discloses at column 5, lines 14-18, that the patent is directed to one type of GIF:

"The present invention relates to substantially pure human antigen-specific GIF with specificity for an antigen associated with an undesirable immune response. This human antigen-specific GIF is highly useful for the immunosuppression of the undesirable immune response in an antigen-specific manner."

Therefore, it is still more suspect that an antibody that binds to this GIF will necessarily bind to MIF. For instance, the antibodies produced in Example 5 of Ishizaka et al. will be specific in their binding to GIF produced in the T-Cell hybridoma CL3. See column 26, lines 1-10. In fact, Ishizaka et al. is directed to producing antibodies that are not only specific in their binding to human GIF, but are even more specific in the antibody binding to the form of GIF described as "antigen-binding GIF." See column 9, lines 9-31, and in particular lines 29-31: "The monoclonal antibodies of the invention can also be used in immunoaffinity chromatography for the purification of the various types of human GIF mentioned herein."

There is extremely little likelihood that antibodies designed to differentiate between forms of GIF would also bind MIF. Even if all or part of the linear sequence might be present on the GIF protein exterior, the folding involved in that protein, in all likelihood, presents different foreign binding sites to those that are presented from the three-dimensional structure of MIF. Although it is within the realm of theoretical possibility that an antibody to one might bind to

another, this does not meet the anticipation by inherency requirement that such a disclosure must necessarily be present.

The possibility that a disclosure may be inherent is not sufficient. See MPEP 2112. The fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic. In re Rijckaert, 9 F.3d 1531, 1534, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993) (reversed rejection because inherency was based on what would result due to optimization of conditions, not what was necessarily present in the prior art); In re Oelrich, 666 F.2d 578, 581-82, 212 USPQ 323, 326 (CCPA 1981). "To establish inherency, the extrinsic evidence must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient." In re Robertson, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999) (citations omitted).

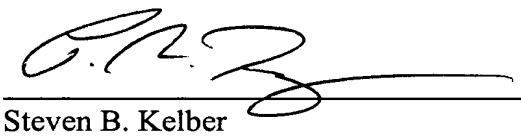
Therefore, Ishizaka et al. fails to anticipate the Claims. Accordingly, reconsideration and withdrawal of the anticipatory rejection is respectfully requested.

CONCLUSION

All rejections having been addressed by the present response, Applicants assert that the present case is in condition for allowance and respectfully request early notice to that effect. If any issues remain to be addressed in this matter which might be resolved by discussion, the Examiner is respectfully requested to call Applicants' undersigned counsel at the number indicated below.

Respectfully submitted,

PIPER RUDNICK LLP



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